REMARKS

Claims 1-60 remain pending in this application, as original claims 61-63 have been canceled. The cancellation is intended to be without prejudice to applicants' right to again present claims having a similar scope in this or a continuing application; no subject matter is being abandoned.

Canceled claims 61-63 were rejected under 35 U.S.C. §112, first paragraph, as not being enabled. Applicants do not agree that there ever was any enablement problem, and are enclosing an information copy of the article "Role of Proton Pump Inhibitors in the Prevention of NSAID-Induced Ulcers Now Emerging," *Drugs and Therapy Perspectives*, Vol. 16, No. 12, pages 6-10 (2000). This article discusses the ability of drugs such as omeprazole and lansoprazole to prevent ulcers. However, since the claims are no longer pending, the rejection is considered moot.

All of the claims stand rejected under 35 U.S.C. § 103(a) as being rendered obvious by the combined teachings of International Published Application WO 96/02535 (called "Larsson et al.") and U.S. Patent 6,262,085 to Whittle et al. Applicants respectfully traverse this rejection in the following discussion.

Larsson et al. disclose a method for directly synthesizing an enantiomer of a substituted sulfoxide, through an asymmetric oxidation. In this synthesis, the starting material is a sulfide having a formula Het_1-X-S-Het_2 and this material is reacted with an oxidizing agent (such as a hydroperoxide) and a chiral titanium complex (such as a titanium IV alkoxide that has been reacted with a tartaric acid ester), optionally in the presence of a base to improve enantioselectivity.

Whittle et al. disclose compounds that are variations of known substituted benzimidazoles, particularly an analog of omeprazole having the methoxy group at the 6-position. This compound is said to co-crystallize with omeprazole, which is similar in structure except for having the 5-methoxy group. Both compounds have two enantiomers, resulting from a chiral center being the S-atom, and the invention includes the enantiospecific synthesis of crystals that have the diastereomers of both compounds

(either S-S or R-R). One embodiment of the synthesis follows the procedure of Larsson et al., as discussed above.

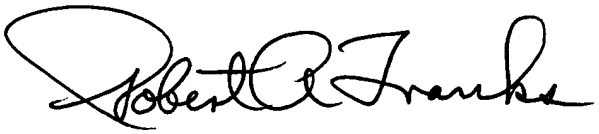
The presently claimed invention differs significantly from the teachings of the two cited documents. The process of independent Claim 1 begins with a racemic sulfoxide, which is not described as a starting material in the process of Larsson et al. or the process of Whittle et al. The racemic sulfoxide is reacted with a coordinating agent containing a transition metal and a chelating agent, to form a racemic mixture of transition metal complexes. Then, that mixture of complexes is reacted with an organic acid or salt that contains a chiral center, to form a racemic mixture in which the component compounds have differing physical properties – such as solubility in a solvent – that enables their separation. This process is common to all of the claims that depend from claim 1, namely claims 2-43.

Independent Claim 44 also differs significantly from the processes of the cited documents. The process begins with a salt of omeprazole, a racemic sulfoxide, while the cited documents disclose processes that can end with salt formation from an enantiomerically pure sulfoxide. Also, the processes of the cited documents form salts from optically pure compounds, while the omeprazole salt specified as the starting material in the applicants' claim is racemic. This process is common to all of the dependent claims 45-60.

An obviousness rejection requires the fulfillment of three criteria: there must be some suggestion or motivation, in the cited documents or general knowledge in the art, to modify a document's teachings or combine teachings; there must be a reasonable expectation of success; and the cited documents must teach or suggest all of the claim limitations. See M.P.E.P. § 706.02(j), citing *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991). None of the three criteria are met using the applied documents, so the rejection does not have a proper foundation and obviousness has not been established. Withdrawal of the rejection, upon reconsideration, is respectfully solicited.

Applicants believe that all of their claims are allowable, so an early notification of allowance is requested. Should any minor matters remain to be resolved for disposition of the application, please contact the undersigned by telephone or facsimile.

Respectfully submitted,



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Role of Proton Pump Inhibitors in the Prevention of NSAID-Induced Ulcers Now Emerging

Drug Ther Perspect 16(12):6-10, 2000.

Introduction

The associations between nonsteroidal anti-inflammatory drugs (NSAIDs) and the presence and complications of gastroduodenal erosions and ulcers are well established. Strategies to reduce NSAID-induced injury include avoidance of NSAIDs or minimising their dosage, selecting NSAIDs known to cause less damage, and co-prescription of various agents, namely cytoprotective or acid suppressing drugs.

Proton pump inhibitors have demonstrated efficacy in the prevention of the adverse gastrointestinal effects of NSAIDs. Omeprazole reduces ulcer rates compared with no treatment, and has clear benefits over the histamine H2 antagonist ranitidine and to a lesser extent over misoprostol (see *Differential features*). It seems that this drug class could soon have an established place in the prevention of NSAID-induced gastrointestinal adverse effects.

Risks of NSAIDs Well Known

The toxic effects of NSAIDs on the upper gastrointestinal tract are a frequent cause of morbidity and even mortality.[6] The majority of patients develop some erosions in the stomach after each dose[7] and, with gastroscopy, about 15 to 25% of patients who have been taking NSAIDs regularly are found to have a discrete ulcer.[7,8] Most ulcers found in this way are asymptomatic and quite small.[7] They presumably heal and reappear a number of times before reaching a threshold for diagnosis in normal practice.

The most important complications of NSAID-induced ulceration of the stomach or duodenum are haemorrhage and perforation.[1] Treatment with NSAIDs increases the risk of these complications by 3 to 10 times,[8] with some particular NSAIDs increasing the risk even more than this.

Apply Common Sense, Minimise Problems

The most obvious way to reduce ulcer risk is to avoid using NSAIDs when they are not necessary.[1] When NSAIDs are required, the lowest effective dosage should be used as there is now good evidence that the risk of ulcer complications is dosage dependant.[9]

As some NSAIDs are more damaging than others, clinicians should consider choosing an agent from the less damaging end of the spectrum unless there is a particular need for one of the more potent agents or formulations.[1] The new highly selective inhibitors of cyclo-oxygenase type-2 (COX-2) offer a further choice, particularly in patients at high risk of NSAID ulceration.[1] Because of their selectivity, these agents cause less gastroduodenal ulceration than those drugs which inhibit both COX-2 and COX-1.[1]

Standard Prophylaxis Has Drawbacks

The co-prescription of cytoprotective or acid suppressing drugs has been shown to be useful in preventing NSAID-induced gastric damage.[1]

Misoprostol Reduces Ulceration . . .

Cytoprotection with a prostaglandin analogue, such as misoprostol, is an effective strategy for reducing NSAID injury and its complications.[1] The approach was developed knowing that prostaglandins are defensive factors in the normal gastric mucosa and that NSAIDs damage the upper gut, at least in part, by inhibiting the production of these mucosal prostaglandins.

In short term studies, misoprostol markedly reduced the number of erosions in the stomach during NSAID therapy.[1] In longer term studies, the drug has been shown to reduce the incidence of gastric and duodenal ulcers by about 60 to 70%.[7,10] The number of episodes of ulcer bleeding over a 6-month period has also been shown to be halved by misoprostol prophylaxis.[11]

. . . but Adverse Effects a Problem

The protective effects of misoprostol are dosage dependant, as are the adverse effects of diarrhoea and abdominal cramps, which occur in about 10% of patients.[1] Diarrhoea associated with misoprostol, in particular, may occasionally be severe and require drug withdrawal.[2] These adverse effects may limit patient compliance with the drug.

H_2 Antagonists Have Limited Efficacy

H_2 antagonists have been shown to reduce the risk of NSAID-induced ulcers; however, their efficacy is limited, at least at standard dosages.[1] For example, although ranitidine 150mg twice daily confers substantial protection against the development of duodenal ulcers during NSAID administration, there is no significant protection against gastric ulcers.[12,13] Gastric ulcers tend to be more of a problem in NSAID users. Similarly, the use of cimetidine doesn't appear to produce any reduction in the incidence of ulcer bleeding.[14]

Higher than standard dosages of H2 antagonists may give improved results.[15] Nevertheless, even at larger dosages these drugs have a fairly modest effect in elevating intragastric pH to levels needed (pH 4 to 5) to reduce the acid component of gastric injury.[1]

Proton Pump Inhibitors a Better Choice?

Proton pump inhibitors are emerging as an effective and well tolerated means of protecting the stomach from NSAID-induced ulceration.[1] These drugs also seem to improve dyspeptic symptoms.[1]

Decreases Ulcer Rates

Short term studies (</=1 month) have demonstrated that co-therapy with the proton pump inhibitors omeprazole and lansoprazole protects against gastric erosions (although it should be noted that it is uncommon for ulcers to develop during such short term administration of NSAIDs).[1]

Results from placebo-controlled studies continued for >/=months have shown a reduction of >70% in overall ulcer rates (gastric plus duodenal) when omeprazole 20 mg/day was co-prescribed with an NSAID.[16,17] Pantoprazole 40 mg/day seemed to confer less marked protection (32% decrease in ulcer rates) in 1 study,[18] but these results were complicated by very high ulcer recurrence rates found in both placebo and active treatment groups.

Data suggest that, as with the H2 antagonists, proton pump inhibitors may protect the duodenum a little better than the stomach.[1] However, differences do not approach statistical significance.

Steps Past Ranitidine in ASTRONAUT

Omeprazole has been shown to be more effective than ranitidine in the Acid Suppression Trial: Ranitidine versus Omeprazole for NSAID-Associated Ulcer Treatment (ASTRONAUT) study (see *Differential features* table 1).[4] Patients with peptic ulcer or >10 gastric or duodenal erosions were recruited to this study which consisted of 2 phases - an initial healing phase and a subsequent maintenance phase. Healing of peptic ulcers was significantly

better with omeprazole 20 or 40 mg/day than with ranitidine 150mg twice daily (80 or 75% *vs* 63%) over 2 months; both dosages of omeprazole were equally efficacious.

Those patients whose lesions were healed entered the maintenance phase of the study. After 6 months, omeprazole 20 mg/day was found to be more effective than ranitidine. More omeprazole recipients stopped treatment because of adverse events (6.1 *vs* 3.2%) but otherwise rates of adverse events were similar.

Similar to Misoprostol in OMNIUM . . .

Misoprostol and omeprazole are effective in the healing and prevention of recurrence of peptic ulcer in patients treated with NSAIDs.[5] Both drugs have similar efficacy at preventing ulcer recurrence in the stomach, but omeprazole appears superior for prophylaxis of duodenal ulcer.

The 2 drugs were compared in the Omeprazole versus Misoprostol for NSAID-Induced Ulcer Management (OMNIUM) study (see *Differential features* table),[5]

a trial which also included a healing phase and a maintenance phase. Omeprazole (20 or 40 mg/day) and misoprostol (200 µg 4 times daily) produced similar overall rates of successful treatment of ulcers, erosions and symptoms at 8 weeks (76 and 75% for omeprazole 20 and 40 mg/day, and 71% for misoprostol) despite higher healing rates with omeprazole, particularly at 20 mg/day. However, misoprostol was more effective at healing erosive disease alone (87% healed *vs* 77 and 77% for omeprazole 20 and 40 mg/day).

In the maintenance phase, those healed were randomised to omeprazole 20 mg/day, misoprostol 200 µg twice daily or placebo for 6 months. Overall, omeprazole was more effective than misoprostol in preventing ulcer recurrence and both drugs were more effective than placebo.

. . . but Better Tolerated

Misoprostol seems to be associated with more adverse effects than omeprazole. Misoprostol was discontinued because of adverse events (e.g. diarrhoea, abdominal pain) significantly more often than either omeprazole or placebo during maintenance therapy (7.7 *vs* 3.9 or 1.9%, respectively).[5]

Future Research Needs

Although it now seems clear that treatment with proton pump inhibitors is able to prevent NSAID-induced upper gastrointestinal injury, further research is required to:[1]

- determine whether all proton pump inhibitors are equally effective at equivalent dosages
- determine the optimally effective dosage of a proton pump inhibitor for preventing ulcers
- confirm the observation that proton pump inhibitors are able to protect against NSAID-induced ulcer complications (e.g. bleeding, perforation)
- determine the cost effectiveness of therapy with proton pump inhibitors (i.e. whether the costs associated with prophylactic medication are offset by savings from reduced medical costs and greater workplace productivity)
- determine whether *Helicobacter pylori* infection constitutes an additional risk factor in patients taking NSAIDs.

Differential Features: Comparison of selected features of some drugs used in the prophylaxis of peptic ulcers induced by nonsteroidal anti-inflammatory drugs (NSAIDs)[1-3]

Feature	Omeprazole	Misoprostol	Ranitidine
Class	Proton pump inhibitors	Prostaglandin analogues	Histamine H2 antagonists
Dosage[a]	20 mg/day	800 µg/day	300 mg/day
Frequency of	Once daily	2-4 times daily	Twice daily

dosage			
Efficacy (percentage of patients in remission):[6]			
ASTRONAUT [4]	72	-	59
OMNIUM [5]	61[d]	48[c,d]	-
Adverse effects	Headache, diarrhoea, hypersensitivity reactions (rash, bronchospasm), pruritus, dizziness, nausea and vomiting, constipation, flatulence, abdominal pain, muscle and joint pain, blurred vision, depression, dry mouth	Diarrhoea,[e] abdominal pain, dyspepsia, flatulence, nausea and vomiting, abnormal vaginal bleeding, rashes, dizziness	Diarrhoea and other gastrointestinal disturbances, altered liver function tests, headache, dizziness, rash, tiredness; occasionally gynaecomastia, impotence
Acquisition cost:[f]			
In the UK (£)	1.02	0.37	0.65
In the US ($)	3.38	1.42	3.12

a Maintenance dosage used in clinical trials.
b Patients remaining in remission 6 months after initial healing of ulcer(s) ≥3mm in diameter or >10 gastric or duodenal erosions.
c $p<0.005$ *vs* omeprazole.
d $p<0.001$ *vs* placebo.
e May occasionally be severe and require drug withdrawal.
f Per day at dosage listed above.
Abbreviations: ASTRONAUT = Acid Suppression Trial: Ranitidine versus Omeprazole for NSAID-Associated Ulcer Treatment; OMNIUM = Omeprazole versus Misoprostol for NSAID-Induced Ulcer Management.

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Sidebar: Regional Considerations in the Prevention of NSAID-Induced Ulcers

In Australia

The recent proton pump inhibitor studies with omeprazole indicate that this class of drugs is efficacious in the prophylaxis of NSAID-induced ulceration (and hence presumably ulcer complications, although this has not been directly studied). All the proton pump inhibitors almost certainly provide similar efficacy. High dose H_2 receptor antagonists are insufficient to protect against gastric ulcer, which is the more common clinical problem than duodenal ulcer related to NSAID use. However, misoprostil in practice is clearly often very poorly tolerated because of diarrhoea and hence acid suppression is preferable. Other data suggest that *Helicobacter pylori* eradication alone provides insufficient protection in terms of ulcer prophylaxis, although the level of protection is greater in those never previously exposed to NSAIDs or who used only aspirin. *H. pylori* eradication may lessen the degree of acid inhibition obtained with antisecretory therapy and result in slower healing of NSAID-induced gastric ulcers but this is clinically not a major issue. In current practice, high risk patients (e.g. >60 years of age with a previous ulcer history or receiving anticoagulants) who are required to take traditional NSAIDs [e.g. inadequate response to cyclo-oxygenase 2 (COX-2) specific NSAIDs or are unable to afford them] should be treated with either full dose misoprostil or, if not tolerated, a proton pump inhibitor (use of which is a problem because of authority requirements) on a long term basis.

Nicholas Talley, *Penrith, NSW*

In Canada

The use of NSAIDs is fairly common in North America. Given the increasing age of our population over time, there will be more patients using these agents who are at increased risk of complications such as ulcer, bleeding or perforation. The concomitant use of agents to protect against these potential effects has thus increased and will continue to do so. H_2 receptor antagonists have not been favoured in this regard because of their inferior efficacy. Although proton pump inhibitors and prostaglandin analogues may have similar ulcer prevention rates, the diarrhoea induced by the required dosages of misoprostol has limited its use. In fact, it is fair to say that, in Canada, proton pump inhibitors have become the main tools for the prevention of NSAID-induced ulcers. Recently, however, the introduction of COX-2 inhibitors has challenged this. With the reduced rates of ulcer and ulcer complications with these agents compared with conventional NSAIDs, COX-2 inhibitors are fast becoming the preferred NSAIDs, particularly in patients at risk of NSAID-gastropathy. Physicians are, however, still uncertain about using these agents without added protection in those at greatest risk, such as patients with previous ulcer complications. Time and further research will tell whether these new agents are cost effective and whether they will live up to their promise of reducing the need for protective agents, such as proton pump inhibitors, during NSAID use.

Carlo A. Fallone, *Montreal, PQ*

In Germany

In an appreciable percentage of cases, the use of systemic NSAIDs is associated with adverse reactions ranging from lesions of the GI mucosa to life-threatening perforations, ulcers and bleeding (PUB). The annual cost in Deutschmarks (DM) of preventing and treating these adverse effects in the German statutory health insurance fund (GKV) has recently been determined as follows: NSAID-associated use of H_2 receptor antagonists (DM31 million), proton pump inhibitors (DM29 million), other antacids and anti-ulcer drugs (DM15 million), antidiarrhoeals and digestants (DM12 million), spasmolytics, anticholinergic and gastroprokinetic agents (DM10 million), anti-ulcer

prostaglandin analogues (DM2 million), antiemetics and antinauseants (DM1 million) and bismuth anti-ulcer drugs (<DM1 million). This compared with 10 700 NSAID-related hospital admissions for PUB in the GKV resulting in 157 000 hospital days and costs of DM125 million.[1] Under current practice, an investment of nearly one-quarter of a billion Deutschmarks (≈US107 million) annually for the management of NSAID-induced adverse events is unable to prevent the occurrence of 1100 to 2200 NSAID-associated deaths per year among approximately 73 million members of the GKV. Selective inhibitors of COX-2 or the comedication of NSAIDs with misoprostol or omeprazole are recommended in the symptomatic treatment of rheumatic diseases in Germany in patients with a high risk of GI events. But still, many practitioners combine NSAIDs with so-called gastroprotective agents which do not prevent PUBs.

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Wolfgang W. Bolten, *Wiesbaden*

In South Africa

The cost of preventing NSAID-induced gastroduodenal adverse events is prohibitive and, as such, the prophylaxis of NSAID-gastropathy varies between state institutions and local private practice. Prophylaxis (i.e. with an H_2 receptor antagonist or omeprazole - the proton pump inhibitor currently on state tender) is not routinely offered to patients in state institutions. It is limited to patients with a history of gastroduodenal toxicity or those taking corticosteroids/ anticoagulants concomitantly. Selective COX-2 inhibitors are not routinely available to high risk patients. Misoprostol, because of its cost and tolerability profile, is seldom used in state institutions. In contrast, the private practice environment follows socioeconomic trends, namely the identification of high risk patients and the use of primary COX-2 inhibitor therapy or nonselective NSAIDs in combination with a proton pump inhibitor. The cost and efficacy of these 2 approaches have not yet been determined.

C. J. van Rensburg, *Cape Town*
